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10/536,809	05/27/2005	Daisuke Tenmizu	08959.0011	4582

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,809	TENMIZU ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed July 26, 2007. Currently, claims 2-14 are pending. Claims 5-7, 12-14 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group I, Claims 1-4 in the paper filed February 2, 2007 is acknowledged.

Claims 5-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Newly submitted claims 12-14 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons.

Inventions of Claims 2-4, 8-10 and Claims 12-14 are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because Claim 12 for example relies upon extensive metabolizers. Whereas Claim 14 relies upon poor metabolizers. The beagles selected in Claim 12 could be selected by a materially different process to obtain the same product. Finally, the subcombination has separate utility such as a method for determining whether beagles metabolize drugs.

The examiner has required restriction between combination and subcombination inventions. A**pplicant elected a subcombination, and claims thereto are subsequently found allowable, any claim(s) depending from or otherwise requiring all the limitations of the allowable subcombination will be examined for patentability in accordance with 37 CFR 1.104. See MPEP § 821.04(a).** Applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 12-14 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This application is a 371 of PCT/JP04/07356, May 28, 2004 and claims priority to Japan 2003-152917, filed May 29, 2003 and Japan 2003/206581, filed August 7, 2003.

It is noted that a translation of the foreign document has not been received.

Drawings

4. The drawings are acceptable.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

6. The specification contains a list of references, pages 6-7.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-4, 8-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for detecting a canine CYP1A2 genetic polymorphism, characterized by determining a base corresponding to a base at position 1117 of a beagle CYP1A2 gene.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. With respect to claims which encompass variants, as provided in Example 11 of the Written Description Guidelines, no common structural attributes identify the members of the genus. Given the broad definition in the specification for a base corresponding to "a base at position 1179 of the nucleotide sequence of SEQ ID NO: 22" the claims encompass mutations and polymorphisms not particularly taught in the instant specification since it is not clear which numbering system is used and what the numbering references. The specification specifically teaches that "corresponding to a base at position 1117 of a canine CYP1A2 gene" is not particularly limited, so long as it is a base at position 1117 of a canine CYP1A2 gene. Namely, it is not necessary for each flanking sequence at either the 5' or 3' side of the lll7th base to accord exactly with that of SEQ ID NO: 22. The specification only describes the 1179 base within SEQ ID NO: 22 and not with a different flanking sequence. Moreover, the specification appears to suggest that any polymorphism within any beagle CYP1A2 gene would be encompassed by the claims. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a base at position 1179 of the nucleotide sequence of SEQ ID NO: 22 is insufficient to teach any base corresponding to a base at position 1117 of any beagle CYP1A2 gene.

There is no description of the mutational sites that exist in nature and there is no description of how the structure of CYP1A2 relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Response to Arguments

The response traverses the rejection. The response asserts the claims have been amended to recite "beagle dog" and "beagle CYP1A2 gene". Further the response asserts that beagle dog sequences are disclosed. This argument has been considered but is not convincing because the specification nor the claims describe the 1117 position. As discussed previously, without a frame of reference for the 1117 position, it is unclear whether the number starts at the cDNA ATG or the genomic sequence or a partial sequence. The 112/2nd indicated that at position 1179 of SEQ ID NO: 22 would have overcome the rejections.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 2-4, 8-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of sequencing the known Dah2 gene from beagles, does not reasonably provide enablement for a method for detecting a canine CYP1A2 genetic polymorphism in any canine and associating the polymorphism with "extensive" and "poor" metabolizers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 2-4 are drawn to methods for determining whether a beagle is an extensive or poor metabolizer by detecting CYP1A2 genetic polymorphisms corresponding to a base at position 1117 of a beagle CYP1A2 gene.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the analysis of CYP1A2 in dogs. Mise (Pharmacogenetics, Vol. 14, pages 769-773, November 2004) teaches CYP1A2 gene mutation C1117 is found in poor metabolizers. Mise moreover teaches that PM dogs were homozygote of the mutant allele and EM dogs were homozygote or heterozygote of the wild-type allele (page 771, col. 1). The post filing date art thus illustrates the importance of heterozygotes and homozygote distinguishments. Mise further points out the interindividual differences associated with genetic and environmental factors. Mise suggests that the detailed characterization of CYP1A2 null dogs is required. Mise states that only beagle dogs were genotypes and there are many breeds of dogs other than beagles. Mise teaches it would be important and interesting for the pharmaceutical field and veterinary fields to investigate the differences in genetic polymorphism of CYP1A2 between various breeds (page 772, col. 2).

Guidance in the Specification.

The specification provides teaches the SNP at position 1117 of a canine CYP1A2 gene (i.e., at position 87 of exon 4) is substituted from C to T. This cases a condon

encoding arginine (Arg) at position 373 of CYP1A2 changes to a stop codon (page 10, para 15) causing CYP1A2 to not be expressed in a dog having a T/T genotype.

A base corresponding to "a base at position 1179 of the nucleotide sequence of SEQ ID NO: 22" is not particularly limited, so long as it is a base at position 1117 of a canine CYPIA2 gene. Namely, it is not necessary for each flanking sequence at either the 5' or 3' side of the lll7th base to accord exactly with that of SEQ ID NO: 22.
The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to being able to practice the claimed invention as broadly as claimed.

Moreover, the claims do not appear to set forth the base associated with metabolization of drugs. The art teaches the C to T polymorphism is located at position 1179 of SEQ ID NO: 22. The poor metabolizers are T/T and the extensive metabolizers are C/C or C/T. Thus, the claims which broadly are drawn to any base sequence do not provide the skilled artisan with guidance how to determine which dogs are extensive metabolizers based on the presence of an A or G, for example.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the difficulties of associating polymorphisms with phenotypes, the broad scope of the claims would require additional, unpredictable experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts the claims have been amended to require beagle. This amendment has overcome the concerns directed to any canine and thus is moot.

The response asserts that the specification teaches a C to T substitution at amino acid position 373. This argument has been considered but is not convincing because the claims do not require a C to T substitution at any particularly identified position. Position 1117 is not definite in its location since nucleic acid numbering systems vary significantly.

The response further asserts that PM dogs are homozygous for the T allele and the EM dogs are heterozygotes or homozygous for the wild-type allele. This argument has been reviewed but is not persuasive because the claims are not directed to this limitation.

The response asserts that Mise supports the enablement of the invention. This argument has been reviewed but is not fully persuasive. Mise discusses the interaction of a C –T substitution at a postion 1117 is associated with metabolizers. But Mise specifically illustrates homozygotes and heterozygotes are important for determining metabolizers.

The response asserts that the A or G substitutions would be reasonably expected to be EM dogs. This argument has been reviewed but is not persuasive. As clearly noted in the response a substitution of a G at position 1117 produces a change in the amino acid sequence to a glycine. The response concludes this is not a stop codone and thus would be expected to be an EM dog. There is no evidence in the specification or the art at the time of filing that the mechanism that creates the poor or extensive metabolizers is the stop codon. The skilled artisan would reasonably expect that any changes in the amino acid sequence would affect the metabolizing abilities of the dog.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2-4, 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 2-4, 8-11 are indefinite over the recitation "a base corresponding to a base position 1117 of a beagle CYP1A2. The claims do not clearly set forth where position 1117 is in relation to. It is unclear what "position 1117" is related to and whether the numbering system begins with exon 1, the ATG site, the translation or transcription site. To overcome this rejection, the applicant could remove the parentheses and references to position 1117. The claim could be directed to position 1179 of SEQ ID NO: 22.

Response to Arguments

The response traverses the rejection. The response asserts that the specification clearly defines "a base corresponding to a base position 1117 of a beagle CYP1A2 gene" as a base corresponding to a base position at 1179 of the nucleotide sequence of SEQ ID NO: 22 (pages 11-12). The response further argues that the specification teaches the full nucleotide sequence of CYP1A2 cDNA. This argument has been reviewed but is not persuasive. Page 12 of the specification specifically states that "A base corresponding to "a base at position 1179 of the nucleotide sequence of SEQ ID NO: 22" is not particularly limited, so long as it is a base at position 1117 of a canine CYPIA2 gene. Namely, it is not necessary for each flanking sequence at either the 5' or 3' side of the lll7th base to accord exactly with that of SEQ ID NO: 22."

Thus, it is clear that the claims are not limited to any particular sequence with out specific limitations. The claim could be amended to require analyzing the base at position 1179 of SEQ ID NO: 22.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 2-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Uchida et al. (Molecular Pharmacology, Vol. 38, pages 644-651, 1990).

A 112/2nd rejection was presented above since it is unclear what the method actually requires. In the event that the claims only require the active process steps claimed, the following rejection is appropriate. It is noted that the instant claims are directed to determining a base corresponding to a base at position 1179 of SEQ ID NO: 22.

Uchida et al. Teaches isolation of cDNAs coding for three different forms of liver microsomal cytochrome P-450 in beagle dogs. Uchida teaches obtaining dog DNA and cloning the sequence. Uchida teaches the nucleotide sequence for the Dah2 gene. As seen below an alignment of instant SEQ ID NO: 22 and the Dah2 sequence of Uchida is

100% identical over the region comprising position 1179 of SEQ ID NO: 22. Thus, Uchida teaches determining the base corresponding to a base at position 1179 of SEQ ID NO: 22 as required by the instant claims.

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Query  1080  ATCTTCCGACACACCTCCTTTGTCCCCTTCACCATCCCCCACAGCACAACAAAGGACACA
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  1173  ATCTTCGGACACACCTCCTTTGTCCCCTTCACCATCCCCCACAGCACAACAAAGGACACA

Query        ACCTTAAAGGGCTTCTACATCCCCAAGGAA  1170
             ||||||||||||||||||||||||||||||
Sbjct  1233  ACCTTAAAGGGCTTCTACATCCCCAAGGAA  1262
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Response to Arguments

The response traverses the rejection. The response asserts that the claims require determining whether the beagle dog is an extensive metabolizer or a poor metabolizer. This argument has been considered but is not convincing because the claim does not differentiate the full scope of metabolizers by any genotype. Thus, once the genotype (i.e. sequencing) is performed, the dogs are either extensive or poor metabolizers. Thus, Uchida inherently does this step. It is noted that Claims 8-11 are specifically drawn to the association of a genotype with the metabolizer status. Here, Uchida does not specifically distinguish a poor v extensive metabolizer. Thus these claims would be free of the art. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

11. **No claims allowable.**

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner

September 6, 2007